Notch signalling regulates fibroblast activation and collagen release in systemic sclerosis

Dees, C ; Tomcik, M ; Zerr, P ; Akhmetshina, A ; Horn, A ; Palumbo, K ; Beyer, C ; Zwerina, J ; Distler, O ; Schett, G ; Distler, J H W

Abstract: BACKGROUND: Dermal fibroblasts from patients with systemic sclerosis (SSc) release excessive amounts of collagen resulting in tissue fibrosis. The molecular mechanisms underlying this pathological activation are incompletely understood. OBJECTIVE: To investigate whether Notch signalling contributes to the uncontrolled activation of fibroblasts in SSc. METHODS: Activation of the Notch pathway was assessed by immunohistochemistry or Western blot for the Notch intracellular domain and the Notch ligand Jagged-1 (Jag-1) and real-time PCR for the target gene hes-1. Differentiation of resting dermal fibroblasts into myofibroblasts was assessed by staining for -smooth muscle actin. The synthesis of collagen was quantified by real-time PCR and Sircol assays. RESULTS: Notch signalling was activated in lesional skin of patients with SSc. The activation persisted in cultured dermal SSc fibroblasts. Stimulation of healthy dermal fibroblasts with recombinant human Jag-1-Fc chimera resulted in an SSc-like phenotype with increased release of collagen and differentiation of resting fibroblasts into myofibroblasts. Consistent with the selective activation of the Notch pathway in dermal SSc fibroblasts, DAPT or siRNA against Notch strongly reduced the basal collagen expression in SSc fibroblasts, but not in fibroblasts from healthy volunteers. CONCLUSION: It was shown that Notch signalling is activated in SSc and plays an important role in fibroblast activation and collagen release. Inhibition of Notch signalling might be an effective strategy to selectively prevent the aberrant activation of SSc fibroblasts.

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Tables

Gender (F/M)	Age (median/range)	Disease subset (limited/diffuse)	Disease duration (median/range)	Medications
11/3	49 years (33-74)	9/5	6 years (1 – 16)	No DMARDs, Corticosteroids or NSAIDs

Supplementary Table 1: Characteristics of SSc patients at date of biopsy for generation of dermal fibroblast cultures. F = female, M = male. The disease subset was determined according to the criteria proposed by LeRoy et al. Disease duration was measured from the onset of the first non-Raynaud symptoms attributable to SSc. DMARDS = (potentially) disease-modifying anti-rheumatic drugs, NSAIDS = non-steroidal anti-inflammatory drugs